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EXAMINER	
FORD, ALLISON M	
ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,955	TRANQUILLO ET AL.	
	Examiner	Art Unit	
	ALLISON M. FORD	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20090410*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response of 3/22/2009 has been received and entered into the application file. Claims 1-58 have been cancelled, and new claims 59-77 have been presented. Claims 59-77 are currently pending in the current application, all of which have been considered on the merits.

All arguments have been fully considered, and are each addressed below, as appropriate. Rejection/objections not repeated herein have been withdrawn.

Priority

The instant application is a national stage filing under 35 USC 371 of PCT/US04/21414, filed 7/1/2004. Acknowledgement is made of Applicants' claims for priority under 35 USC 119(e) to U.S. provisional applications 60/484,563, filed 7/1/2003, and 60/484,595, filed 7/2/2003.

Oath/Declaration

The supplemental Application Data Sheet submitted with the response has been received and entered into the application file. The ADS provides the information previously omitted, and is accepted.

Information Disclosure Statement

The information disclosure statement submitted with the response has been received and entered into the application file. An initialed copy of the information disclosure statement is being provided with this office action. Certain references were 'lined-through' on the information disclosure statement were not considered because no copies of the references were provided, specifically Applicants cited numerous unpublished US applications, yet did not provide legible copies of each, as is required by 37 CFR 1.98(a)(iii).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Cancellation of claims 2-6, 13, 14, 16, 20, 27 and 46 has rendered the rejections thereof under 35 USC 112, second paragraph, moot. The following rejections are applicable to the newly presented claims:

Claim 76 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 76 is rejected as lacking antecedent basis for the limitation "said factors" in line 5 of the claim; no factors were previously recited in the claim. It is noted that the following line of claim 76 (line 6) does recite "one or more factors capable of permeating the support", it would be remedial to simply switch the order of these limitations:

"An in vitro composition, comprising endothelial cells and smooth muscle cells in combination with a matrix, said matrix in combination with said endothelial cells and smooth muscle cells being circumferentially positioned around a tubular support, wherein one or more factors capable of permeating the support are present within the support, wherein neither sad endothelial cells in combination with the matrix nor said smooth muscle cells in combination with the matrix are exposed to said factors prior to combining both said endothelial cells and smooth muscle cells with said matrix, and wherein said factors are comprised of:

i) one or more mitogenic factors and one or more attractant factors; and/or

ii) one or more mitoattractant factors."

Double Patenting: Duplicate Claim Warning

Applicant is advised that should claim 68 be found allowable, claim 76 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

The only difference between claims 68 and 76 is that claim 68 recites: "the area inside said tubular support containing one or more factors, wherein said tubular support allows said one or more factors to move from the inside of said tubular support to said endothelial cells and smooth muscle cells in combination with said matrix…" whereas, claim 76 recite: "wherein one or more factors capable of permeating the support are present within the support..."

The scope of claims 68 and 76 are considered to be identical. The language of claim 76, while less detailed than 68, still requires one or more factors to be present within the support, and for those factors to be able to permeate through the support material to the matrix and cells located circumferentially around the support material. Thus the claims are identical in scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

New claims 59-67 and 77 replace previous claims 2-6, 13, 14, 16, 20 and 57, respectively. New independent claims 59 and 77 require that neither the endothelial cells nor the smooth muscle cells be exposed to the one or more factors prior to both cell types coming into contact with the matrix. This

limitation is interpreted as requiring the endothelial cells and the smooth muscle cells to simultaneously be exposed to the one or more factors contained within the matrix. This may be achieved by either administering the two cell types simultaneously, or administering the two cell types sequentially, but delaying exposure to the one or more factors until both cell types are present in the matrix.

This limitation does differentiate over the method of Niklason et al, as Niklason et al culture the smooth muscle cells on the support (in contact with the culture medium) for a period of eight weeks prior to seeding the endothelial cells; thus the smooth muscle cells were exposed to the factors present in the culture medium before the endothelial cells were combined with the matrix. Therefore the rejection of record is not upheld over new claims 59-67 and 77.

New claims 68-77 replace previous claims 28-32, 39, 40, 46 and 55, respectively. New independent claims 68 and 77 are directed to compositions comprising endothelial cells and smooth muscle in combination with a matrix circumferentially positioned around a tubular support, wherein one or more factors are contained within the interior area of the tubular support, and for the tubular support to be permeable to the factors so that the factors may move from inside the support to the cells and matrix. The one or more factors are defined as either i) one or more mitogenic factors and one or more attractant factors and/or ii) one or more mitoattractant factors.

While the claims state that neither the endothelial cells nor the smooth muscle cells are exposed to the one or more factors prior to combining the cells with the matrix, this limitation is considered to be a product-by-process limitation which does not structurally affect the claimed composition. Product-by-process limitations are taken into consideration only as far as the process of making imparts distinct structural limitations to the product; yet if the specific structural limitations imparted by the process of making are found in the prior art product, the claims are still considered unpatentable over the prior art.

In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985), and *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979).

It is understood that Applicants are intending to require the cells to be administered simultaneously, and then to subsequently migrate into distinct layers, as opposed to the method of Niklason et al, which involves sequentially applying the cells as distinct layers; however, both methods result in the same distinct cell layers, and thus the final product of Niklason et al is the same as that claimed, even though it is made by a different process. Therefore the rejection of record is applied to new claims 68-74 and 76.

Please further note the claims only state the matrix is "in combination with endothelial cells and smooth muscle cells," the claim does not limit the organization of the endothelial cells and smooth muscle cells as being intermixed, combined, or in non-distinct layers, such as the cells may be upon initial application in the method of the current invention, but rather the claims merely requires the cells to be 'in combination' with the matrix, distinct layers (as in Niklason et al) does read on 'a matrix in combination with endothelial cells and smooth muscle cells'.

Claims 68-74 and 76 are rejected under 35 U.S.C. 102(b) as being anticipated by Niklason et al (Science, 1999), in light of Henrikson (Ed.) Histology. (1997) and Freshney (Ed.) Culture of Animal Cells: A Manual of Basic Technique. (2000).

Niklason et al disclose tissue engineered blood vessels (TEBVs) comprising a tubular, biodegradable mesh scaffold of polyglycolic acid (PGA), around which layers of endothelial cells (ECs) and a layer of smooth muscle cells (SMCs) are provided. Culture medium, comprising DMEM and 20% FBS, is pulsated through the lumen of the tubular scaffold (See Niklason et al, Pg. 490, col. 2-3 & Fig. 1).

The PGA scaffold is considered to read on a tubular support.

Smooth muscle cells naturally secrete type IV collagen (See Henrikson et al, Histology, page 98) which serves as a matrix; thus the SMCs and the ECs are considered to be 'in combination' with a matrix which is circumferentially positioned around the PGA tubular support.

The culture medium flowing through the PGA scaffold (tubular support) contains serum; serum contains at least EGF, PDGF, IGF-1, IGF-2, FGF and transferrin (See Freshney, Pg. 100, Table 8.5), each of these factors are disclosed as mitoattractant factors in the specification (Specification at Pg 12); thus one or more mitoattractant factors is present within the tubular support. Due to the permeability of the PGA scaffold, the one or more factors are permitted to move from the inside of the support to the cells of the TEBV.

Therefore the TEBV of Niklason et al anticipates the subject matter of claims 68, 74 and 76.

The source of the cells, as recited by claims 69-73, are submitted to be product-by-process limitations. As discussed above, product-by-process limitations are considered only insofar as the method of production (or in the instant case, the original source of the cells) imparts distinct structural characteristics or properties to the product being claimed (in the instant case, the ECs and SMCs used in the blood vessel). In the instant case, requiring the ECs and SMCs to be *derived* from stem cells does not impart any structural distinction to the adult ECs or SMCs; in fact, it is submitted all cells are ultimately *derived* from stem cells. Therefore, the source of the cells does not differentiate over the teachings of Niklason et al, and claims 69-73 are properly included in the rejection of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 68-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niklason et al (Science, 1999), in light of Henrikson (Ed.), Histology (1997) and Freshney (Ed.) Culture of Animal Cells: A manual of basic technique. (2000), and in view of Tu et al (US Patent 6,506,398).

The teachings of Niklason et al, Henrikson and Freshney are set forth above. Niklason et al disclose TEBVs that anticipate the composition of claims 68-74 and 76.

Niklason et al differs from the current invention in that they do not disclose vascular endothelial growth factor (VEGF) in the culture media which flows through the tubular support. However, it is submitted that inclusion of VEGF in culture media for a tissue engineered blood vessel construct comprising endothelial cells would have been *prima facie* obvious to one of ordinary skill in the art because use of VEGF with tissue engineered blood vessels was well known in the art, see Tu et al.

Tu et al clearly disclose VEGF to be a mitogenic factor for vascular endothelial cells, and suggests inclusion of VEGF in vascular grafts to enhance vascular endothelial cell recruitment and proliferation (See Tu et al, abstract & col. 4, ln 1-11). Therefore the artisan of ordinary skill would have been motivated to include VEGF in the culture media utilized by Niklason et al in order to improve the EC patency within the graft. One would have had a reasonable expectation of successfully utilizing

VEGF based on the express teachings of Tu et al. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 59-67 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shum-Tim et al (Ann Thorac Surg, 1999), in light of Henrikson (Ed.) (Histology, 1999), and taken in view of Dunkelman et al (US Patent 5,792,603), and further in view of Mitchell et al (Cardiovascular Pathol, 2003) and Hall et al (US Patent 6,387,663).

Shum-Tim et al disclose development of tissue-engineered vascular graft comprising seeding a mixture of endothelial cells, smooth muscle cells and fibroblasts onto a polymeric scaffold. The cells are cultured on the scaffold for seven days, and then implanted as an aortic replacements (See Shum-Tim et al, Pg. 2298-2299 "Materials and Methods: Cell Isolation").

In the method of Shum-Tim et al the polymeric scaffold is considered to read on the matrix of the claimed invention. The cells are seeded onto the matrix as a mixed population, thus none of the cells are cultured on the matrix or contacted with any growth factors prior to all cells being present on the matrix.

Smooth muscle cells naturally secrete type IV collagen (See Henrikson et al, Histology, page 98); thus, upon culture the smooth muscle cells secrete collagen into the matrix, and thus the matrix further comprises collagen.

The source of the cells, as recited by claims 60-64, are submitted to be product-by-process limitations. As discussed above, product-by-process limitations are considered only insofar as the method of production (or in the instant case, the original source of the cells) imparts distinct structural characteristics or properties to the product being claimed (in the instant case, the ECs and SMCs used in the blood vessel). In the instant case, requiring the ECs and SMCs to be *derived* from stem cells does not impart any structural distinction to the adult ECs or SMCs; in fact, it is submitted all cells are ultimately

derived from stem cells. Therefore, the source of the cells does not differentiate over the teachings of Shum-Tim et al, and claims 60-64 are properly included in the rejection of record.

Shum-Tim et al differs from the instant invention in that they do not disclose details of the seven day culture period which occurs after cell seeding and before implantation of the tissue-engineered vascular graft. Specifically, Shum-Tim et al do not disclose circumferentially positioning the cell-seeded matrix around a tubular support, through which one or more factors are contained, and culturing thereupon.

Dunkelman et al disclose an apparatus for culturing a vascular graft comprising a perfusion system which includes a porous tube (48) onto which a vascular graft may be circumferentially positioned around; perfusate is circulated through the system, and specifically through the porous tube (48); the porous tube permits transfer of the perfusate from within the tube to the vascular graft to achieve culture of the vascular graft. The porous tube (48) may be comprised of a porous polymer, such as PTFE (Teflon), PVC, or polycarbonate (porous plastics). (See Dunkelman et al, col. 4, ln 54-col. 5, ln 21).

It is submitted that one of ordinary skill in the art would have found it *prima facie* obvious to use the apparatus of Dunkelman et al to carry out the seven day culture of the cell-seeded polymer scaffold in the method of Shum-Tim et al. The rationale for this conclusion of obviousness is that means for enhancing a particular method (the culture method of Shum-Tim et al) has been made part of the ordinary capabilities of one skilled in the art based upon the teachings of such improvements in other situations (specifically the perfusion system of Dunkelman et al). One of ordinary skill in the art would have been capable of applying the perfusion system of Dunkelman et al (the "enhancement") to the method of Shum-Tim et al (the "base method") and the results would have been predictable to one of ordinary skill in the art, specifically: successful development of the tissue engineered vascular graft of Shum-Tim et al. See *KSR International Co. v Teleflex, Inc. 550 US___, ____, 82 USPQ2d 1385, 1395-97 (2007).*

Shum-Tim et al also differs from the instant invention in that they do not disclose one or more mitogenic factors in combination with one or more attractant factors, or one or more mitoattractant factors being provided in the inside of the support tube.

However, though Shum-Tim et al do not provide the details of the culture conditions in which the vascular graft is produced, it is submitted that it was known in the art that formation of a confluent endothelium prior to implantation was critical for patency of tissue engineered vascular grafts (See Mitchell et al, Pg. 59-60 "Endothelium"). It was further known that VEGF functions as a mitoattractant factor that serves to promote endothelialization of vascular grafts by promoting migration and proliferation of endothelial cells (See Hall et al, col. 19, ln 30-40).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to perfuse the tissue engineered vascular graft of Shum-Tim et al, on the perfusion system of Dunkelman et al, with culture medium comprising VEGF in order to promote migration of the endothelial cells seeded within the scaffold to the luminal surface, and then to promote proliferation of the endothelial cells to form a confluent endothelium within the vascular graft. One would have had reasonable expectation of successfully including VEGF in the perfusion system because VEGF was readily available to the artisan (see, e.g. Hall et al), and its effects on endothelial cells were well documented (again, see Hall et al). The motivation to include VEGF in a culture medium which flows through the porous tubular support comes from the fact that development of a mature, confluent endothelium is critical for patency of the graft upon implantation (See Mitchell et al).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Primary Examiner, Art Unit 1651